General

Guideline Title

Guideline on the prevention of secondary central nervous system lymphoma.

Bibliographic Source(s)

McMillan A, Ardeshna KM, Cwynarski K, Lyttelton M, McKay P, Montoto S. Guideline on the prevention of secondary central nervous system lymphoma: British Committee for Standards in Haematology. Br J Haematol. 2013 Oct;163(2):168-81. [74 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Definitions for the quality of the evidence (A–C) and strength of recommendations (strong [grade 1], weak [grade 2]) are given at the end of the "Major Recommendations" field.

Defining High-risk Groups

Central nervous system (CNS) directed therapy should be offered to patients with high-grade non-Hodgkin lymphoma (NHL) *AND* either:

- A raised (above institutional upper limit of normal [ULN]) serum lactate dehydrogenase (LDH) *AND* *more than one* extra-nodal localisation (noting that the spleen is not regarded as an extra-nodal site and also, two lesions within the same system [e.g., bilateral lung lesions] are regarded as a single extra-nodal localization).
  OR
- Anatomical sites: testicular, breast and epidural
  (Level of evidence: 1B)

Use of Intrathecal (IT) Prophylaxis

All patients requiring CNS-directed therapy should receive 3 to 6 doses of IT methotrexate (MTX) (flat dose of 12–15 mg each dose) during primary therapy, which should be commenced as early as practical during treatment and given at least once per cycle (Level of evidence: 2C).

CNS Prophylaxis with Systemic Chemotherapy

- Systemic high-dose methotrexate (HD-MTX), given at a dose of 3–5 g/m^2, with folinic acid rescue, can also be considered as additional CNS-directed therapy in high risk patients. This should be given strictly in line with published schedules and considered in the context of

performance status and renal function. The benefit of the additional or alternative use of HD-MTX must be carefully balanced against the risk of toxicity and the resource utilisation consequences of the schedule (Level of evidence: 2B).

- There are no data to confirm that HD-MTX alone can replace IT therapy and if this strategy is followed it is essential that the practice is carefully audited (Level of evidence: 2C).
- For the delivery of intravenous HD-MTX, the use of rapid infusion schedules can be recommended, although the authors acknowledge lack of consensus on this issue (Level of evidence: 2B).
- If given without IT chemotherapy, systemic prophylaxis should be commenced as early as practical during treatment without compromising delivery of rituximab-cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) chemotherapy (Level of evidence: 1B).
- Further studies to determine the benefit of systemic and/or IT therapy for the prevention of secondary CNS lymphoma are warranted (Level of evidence: 2C).
- The use of systemic agents other than HD-MTX as CNS prophylaxis in addition to or instead of IT chemotherapy and/or HD-MTX have not been shown to be beneficial. Their use is therefore not recommended except where they form part of an established multi-agent regimen or as part of a clinical trial (Level of evidence: 1C).

Recommendations Specific to Primary Testicular Lymphoma

Patients with primary testicular lymphoma should receive 4 or more doses of IT MTX during primary chemotherapy as per the International Extranodal Lymphoma Study Group (IELSG) protocol (Level of evidence: 2B).

Summary and Recommendations

Given that the evidence supporting any single approach is less than strong, it is recommended that patients should be entered in to prospective randomised controlled trials where available, and, in all other settings, prospective audit of practice should be performed to support the approaches taken. Such audit should record not only the nature of prophylaxis administered, but also the type of CNS relapse and if there is any evidence of concurrent systemic relapsed disease (Level of evidence: 2C).

Definitions:

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series, or just opinion.

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Secondary central nervous system lymphoma

Guideline Category

Management

Prevention

Clinical Specialty

Hematology

Internal Medicine

Oncology

Preventive Medicine

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide healthcare professionals with clear guidance on the optimal prevention of secondary central nervous system lymphoma

Target Population

Patients undergoing first line therapy for lymphoma who are at risk for secondary central nervous system lymphoma

Note: The guidance may not be appropriate to patients with all lymphoma sub-types.

Interventions and Practices Considered

1. Intrathecal (IT) methotrexate (MTX)
2. Systemic/intravenous high-dose methotrexate (HD-MTX)
3. Folinic acid rescue

Note: The use of systemic agents other than HD-MTX as central nervous system (CNS) prophylaxis in addition to or instead of IT chemotherapy and/or HD-MTX is not recommended except as part of an established multi-agent regimen or as part of a clinical trial.

Major Outcomes Considered

- Risk of secondary central nervous system (CNS) lymphoma according to anatomical sites of involvement and clinical factors
- Incidence and timing of CNS relapse

- Efficacy of CNS relapse prevention (e.g., measured by incidence of CNS relapse and survival)
- Treatment-related toxicity

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Ovid MEDLINE, EMBASE, and National Center for Biotechnology Information (NCBI) PubMed were searched systematically for publications in English from 1980–2012 using the Medical Subject Headings (MeSH) subheading "lymphoma, CNS", "lymphoma, central nervous system", "lymphoma, high grade", "lymphoma, Burkitt's", "lymphoma, lymphoblastic" and "lymphoma, diffuse large B cell" as keywords, as well as all subheadings.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series, or just opinion.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to quote levels of evidence (see the

"Rating Scheme for the Strength of the Evidence" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The writing group produced the draft guideline which was subsequently revised by consensus by members of the Haemato-oncology Task Force of the British Committee for Standards in Haematology.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to quote grades of evidence (see the "Rating Scheme for the Strength of the Recommendations" field).

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The guideline was reviewed by a sounding board of approximately 50 UK haematologists, the British Committee for Standards in Haematology (BCSH), and the British Society for Haematology Committee and comments incorporated where appropriate.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate prevention of secondary central nervous system lymphoma

Potential Harms

Intrathecal (IT) Chemotherapy

IT chemotherapy is not without clinical risk and toxicity. Delivery of inappropriate chemotherapy to the cerebrospinal fluid can have fatal consequences and strict control measures must be in place to ensure safe delivery of IT therapy. In the UK, following a number of serious incidents where vinca alkaloids were administered intrathecally, the UK Government Department of Health has issued guidance on safe procedures for the administration of IT therapy (UK Department of Health, 2011) which must be followed. Complications of IT therapy delivered via the lumbar route include headache, arachnoiditis, and encephalitis. Technical difficulties may also occur due to obesity, anatomical variation, and previous spinal surgery which can render the lumbar approach difficult or impossible. The use of Omaya reservoirs inserted at neurosurgical procedures may solve this problem but they are rarely used and have potentially serious complications, especially if they become infected.

Administration of Methotrexate (MTX)

The pharmacology and potential toxicity of MTX are complicated, and subject to large inter-individual differences, and this is summarized well in a recent review. Important variables for both efficacy and toxicity are the dose of MTX, duration of infusion, and the dose and timing of folinic acid rescue, as these influence peak concentrations and exposure time. Thus millimolar concentrations of MTX for minutes or hours may lead to acute renal, central nervous system, and liver toxicity, whereas concentrations of 0.05–0.1 μmol/l for more than 24–48 hours will result in haematological and gastrointestinal toxicity. See the "Administration of Methotrexate" section in the original guideline document for additional details.

Qualifying Statements

Qualifying Statements

- While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.
- The guidance may not be appropriate to patients with all lymphoma sub-types and in all cases individual patient circumstances may dictate an alternative approach.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Oct

Guideline Developer(s)

British Society for Haematology Guidelines - Professional Association

Source(s) of Funding

British Committee for Standards in Haematology

Guideline Committee

British Committee for Standards in Haematology Writing Group

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

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Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the British Journal of Haematology Web site .

Print copies: Available from the British Committee for Standards in Haematology; Email: bcsh@b-s-h.org.uk.

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on October 18, 2013.

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